

Professional Background

- University of Illinois at Chicago
 - Director, Center for Health Statistics
 - Professor of Biostatistics, Psychiatry, and Mathematics, Statistics, and Computer Science
- Ph.D., Statistics and Psychometrics
(University of Chicago, 1981)
- Author, more than 200 peer-reviewed scientific papers, five books

Professional Recognition

- Harvard Award for Lifetime Contributions to Psychiatric Epidemiology and Biostatistics (2003)
- Outstanding Statistical Application Award for Contribution to Drug Safety, American Statistical Association (2009)
- Youden Award, American Statistical Association for Statistical Contributions to Chemistry (2001, 2006)
- Fellow, American Statistical Association
- Member, Institutes of Medicine (IOM), National Academy of Sciences (NAS)
- FDA Advisory Board on Suicide and Antidepressants in Adolescents (2004); Safety Science Board, FDA Sentinel Network (2010)
- National Institutes of Mental Health (NIMH), Research Scientist Award (1995-2000)
- Veterans Administration, Blue Ribbon Working Group on Suicide Prevention (2008)

Dr. Gibbons' Opinions

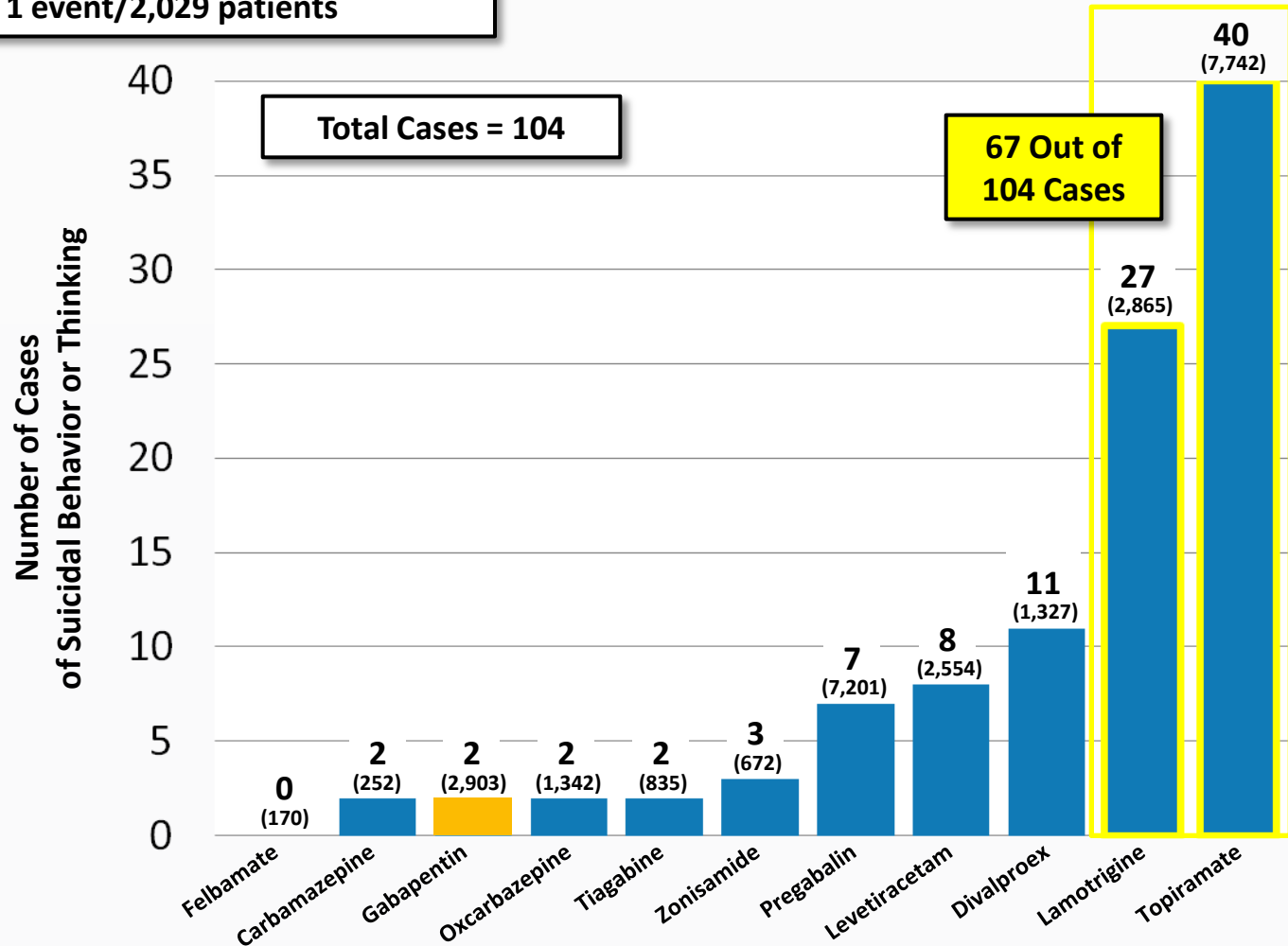
- FDA study does not show that gabapentin causes suicidal thoughts or behavior
- Published AED study in bipolar patients: Shows 11 AEDs in the FDA study, including gabapentin, do not increase the risk of suicide attempts
- Gabapentin study: Gabapentin does not increase the risk of suicide attempts in any patient group
- There is no statistical basis for a gabapentin suicide warning

Dr. Gibbons' Criticisms of FDA 2008 Study

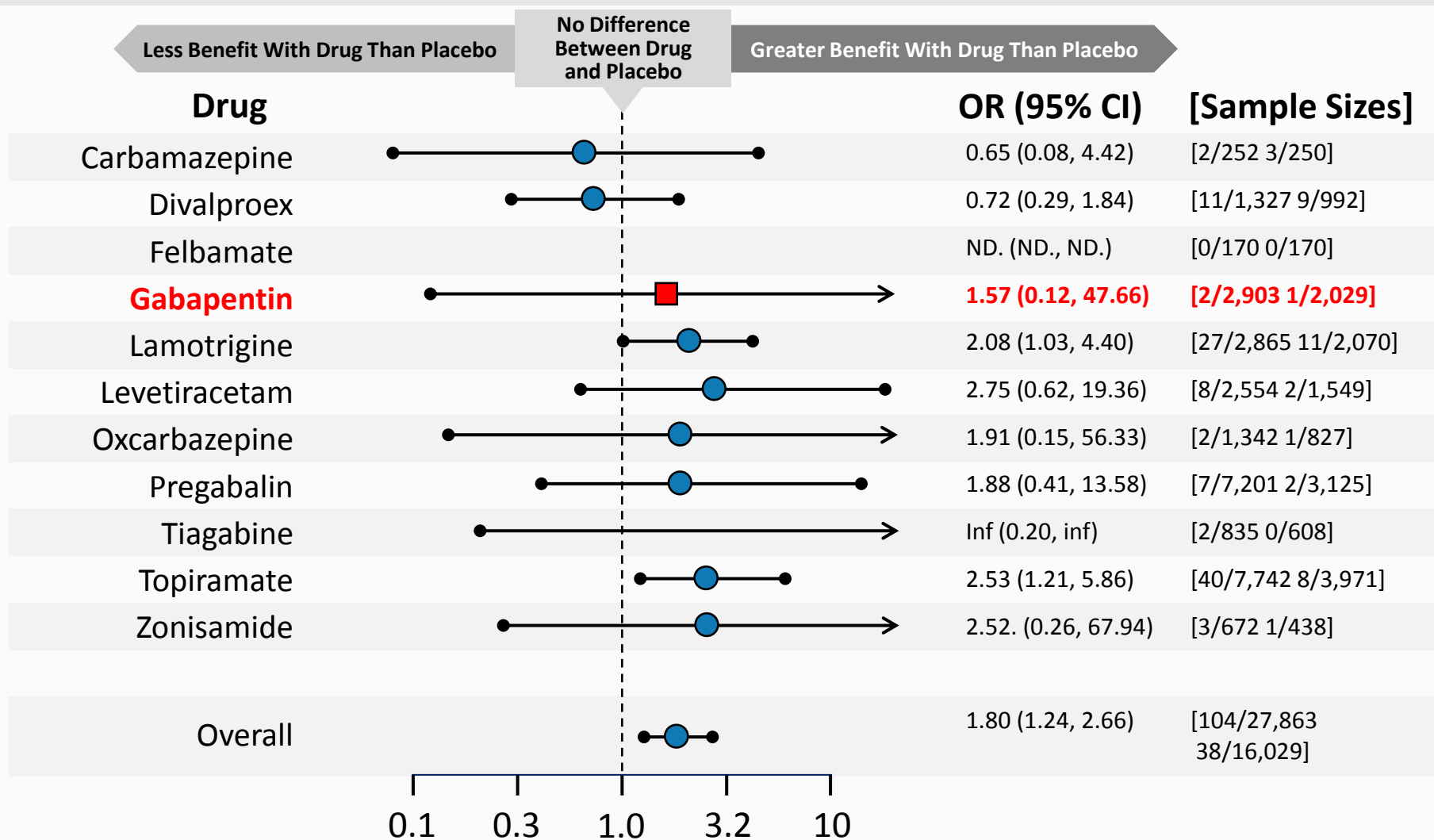
- FDA finding of increased risk was driven by two drugs – topiramate and lamotrigine
- FDA excluded all studies with zero events
- FDA's conclusions regarding increased risk of AEDs cannot be applied to gabapentin
- FDA's conclusions regarding increased risk of AEDs do not apply to all patients

FDA Cases of Suicidal Thinking or Behavior by Drug

Gabapentin studies – placebo treatment:
1 event/2,029 patients

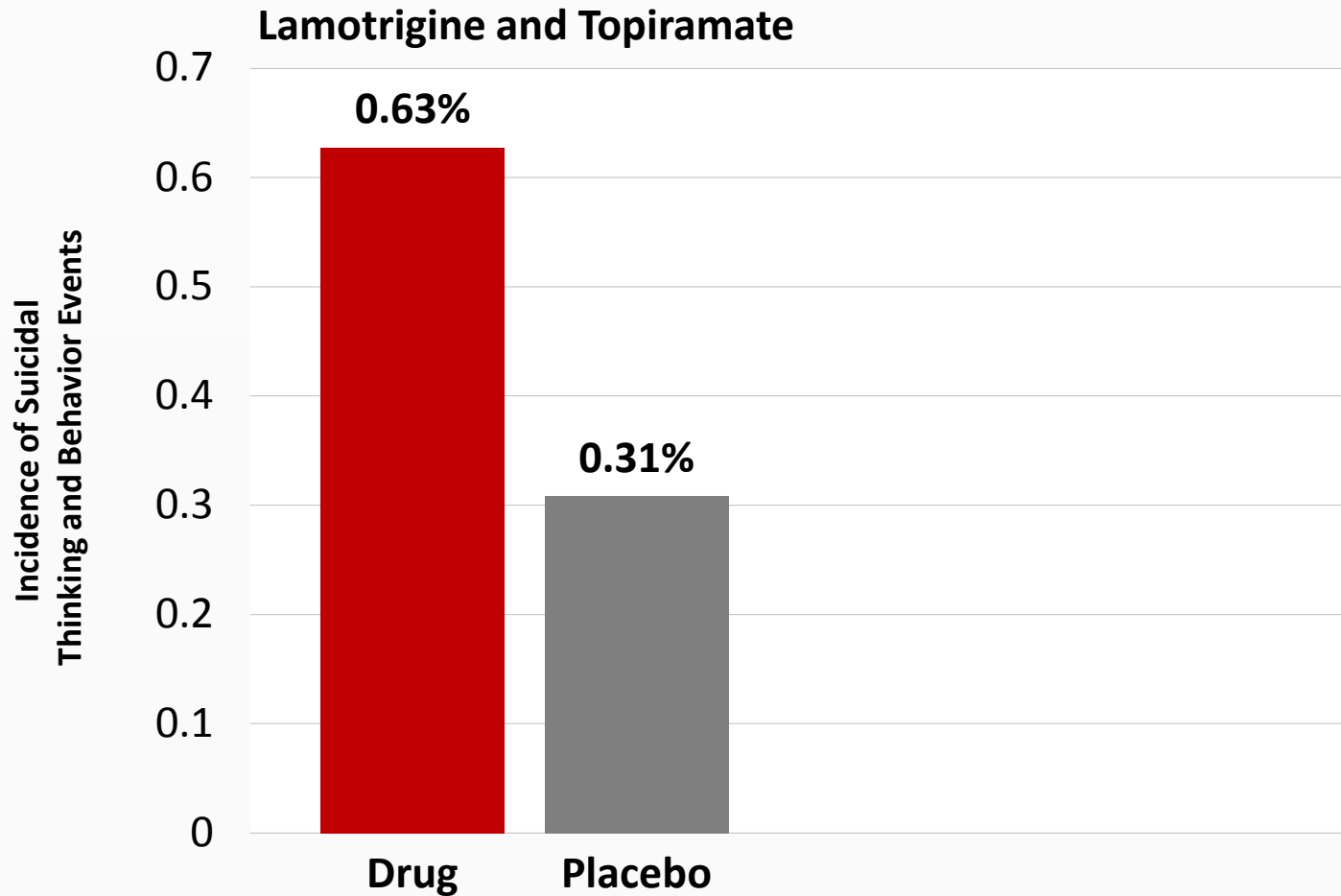


FDA Meta-Analysis: Odds Ratios for All AEDs

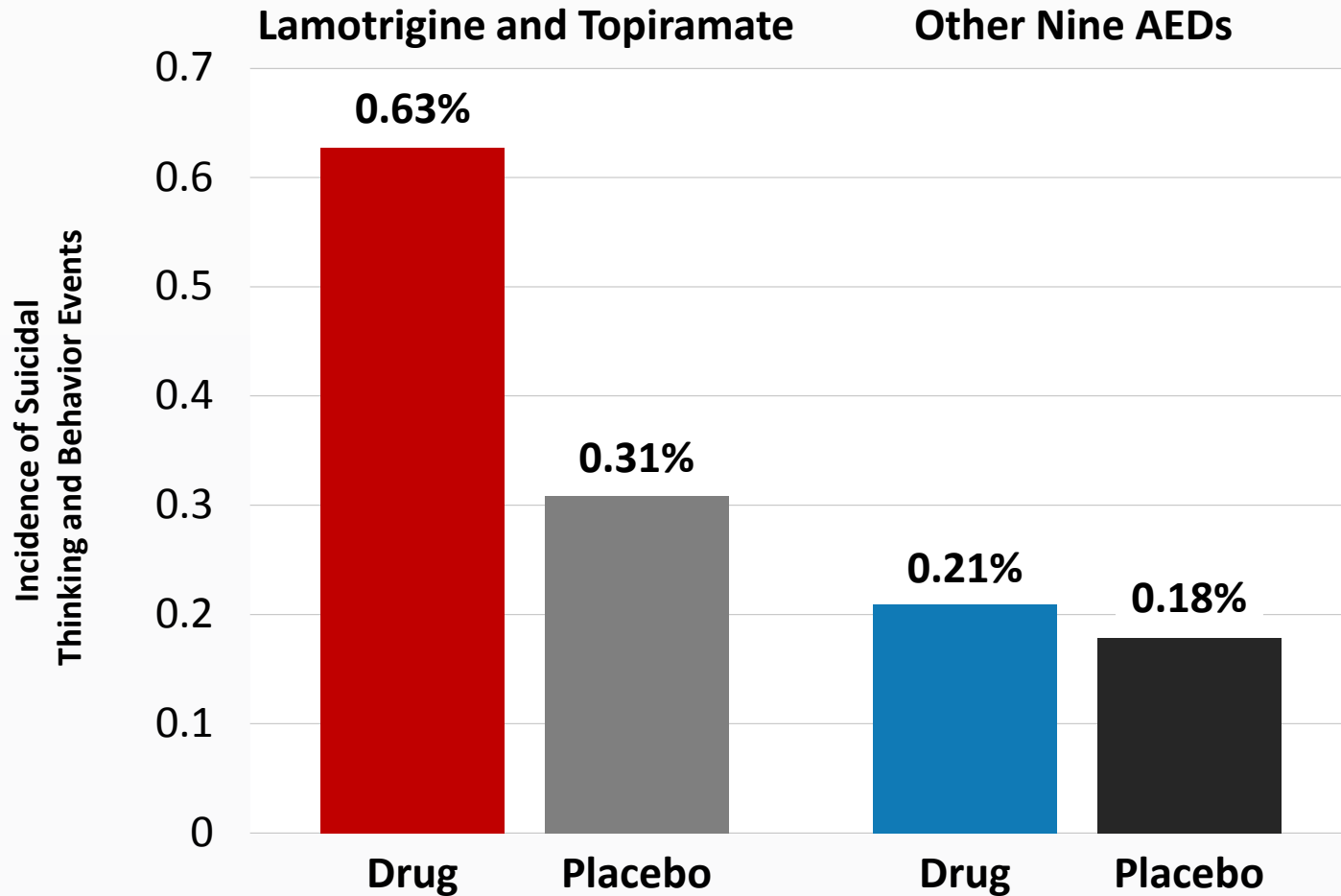


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Source: Based on May 23, 2008 FDA Statistical Review and Evaluation of Antiepileptic Drugs and Toxicity, Figure 2, Pg. 24

Rate of Suicidal Thinking and Behavior for Topiramate and Lamotrigine vs. Other Nine AEDs

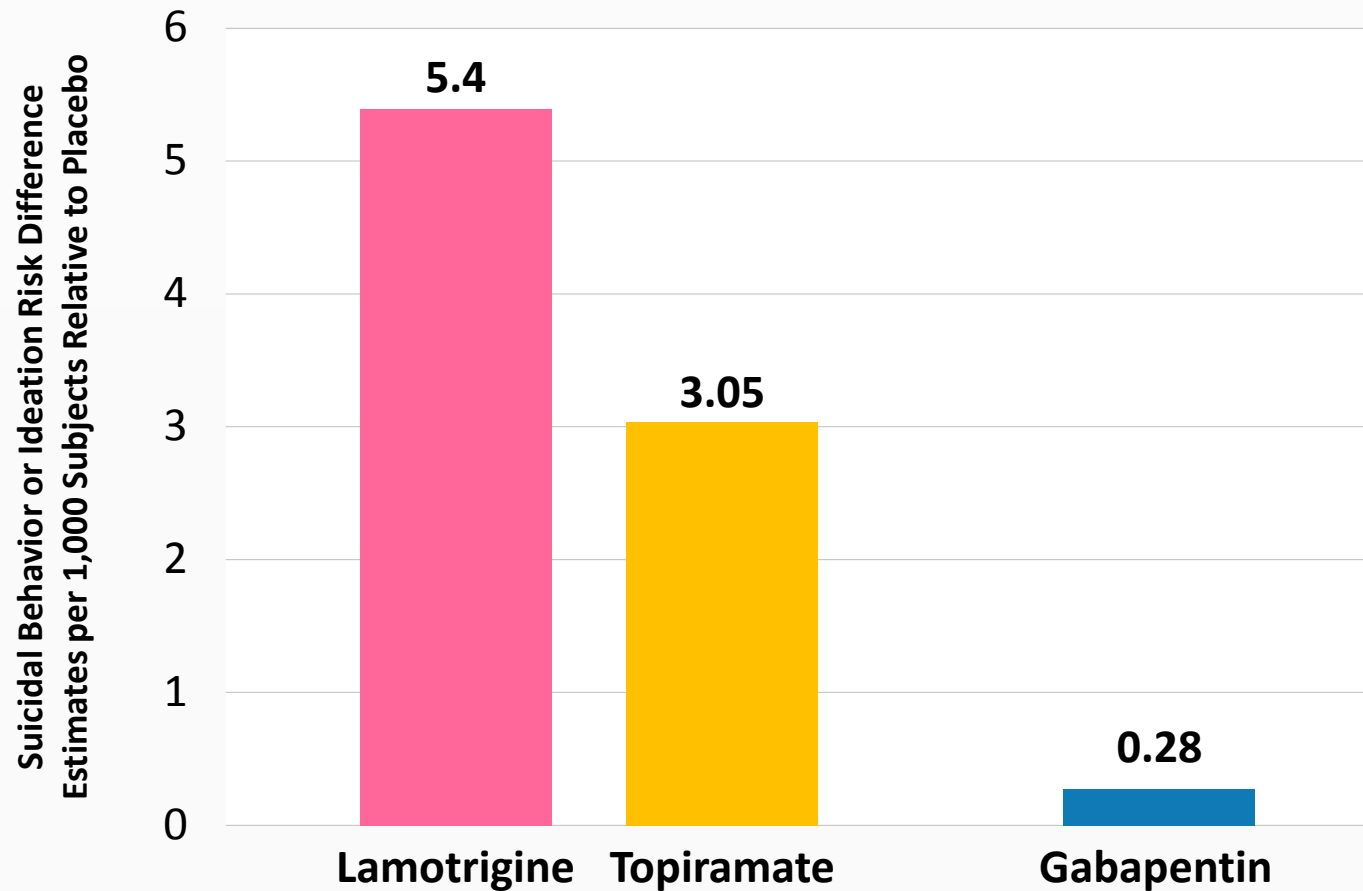


Rate of Suicidal Thinking and Behavior for Topiramate and Lamotrigine vs. Other Nine AEDs

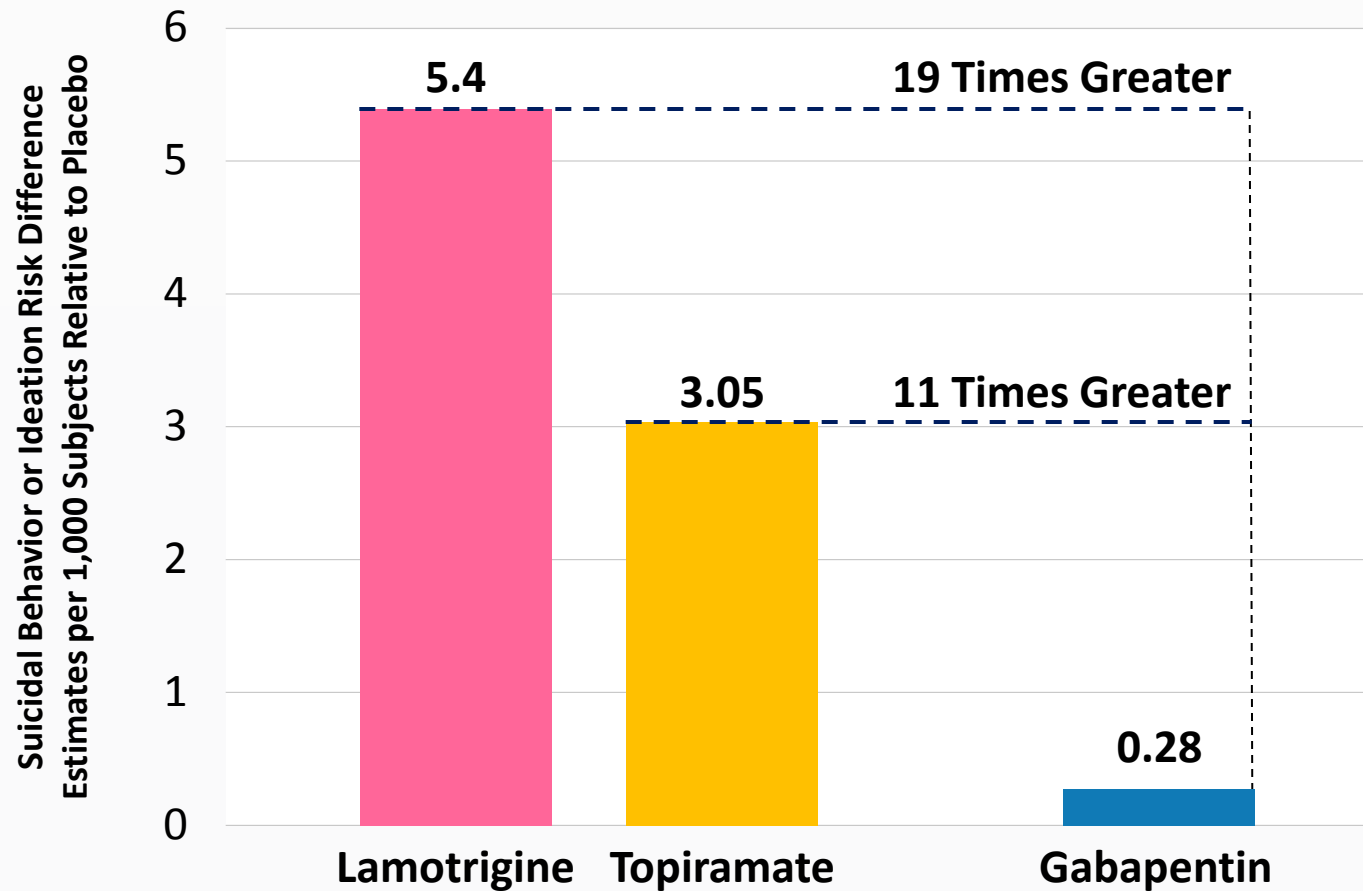


Gabapentin vs. Topiramate and Lamotrigine

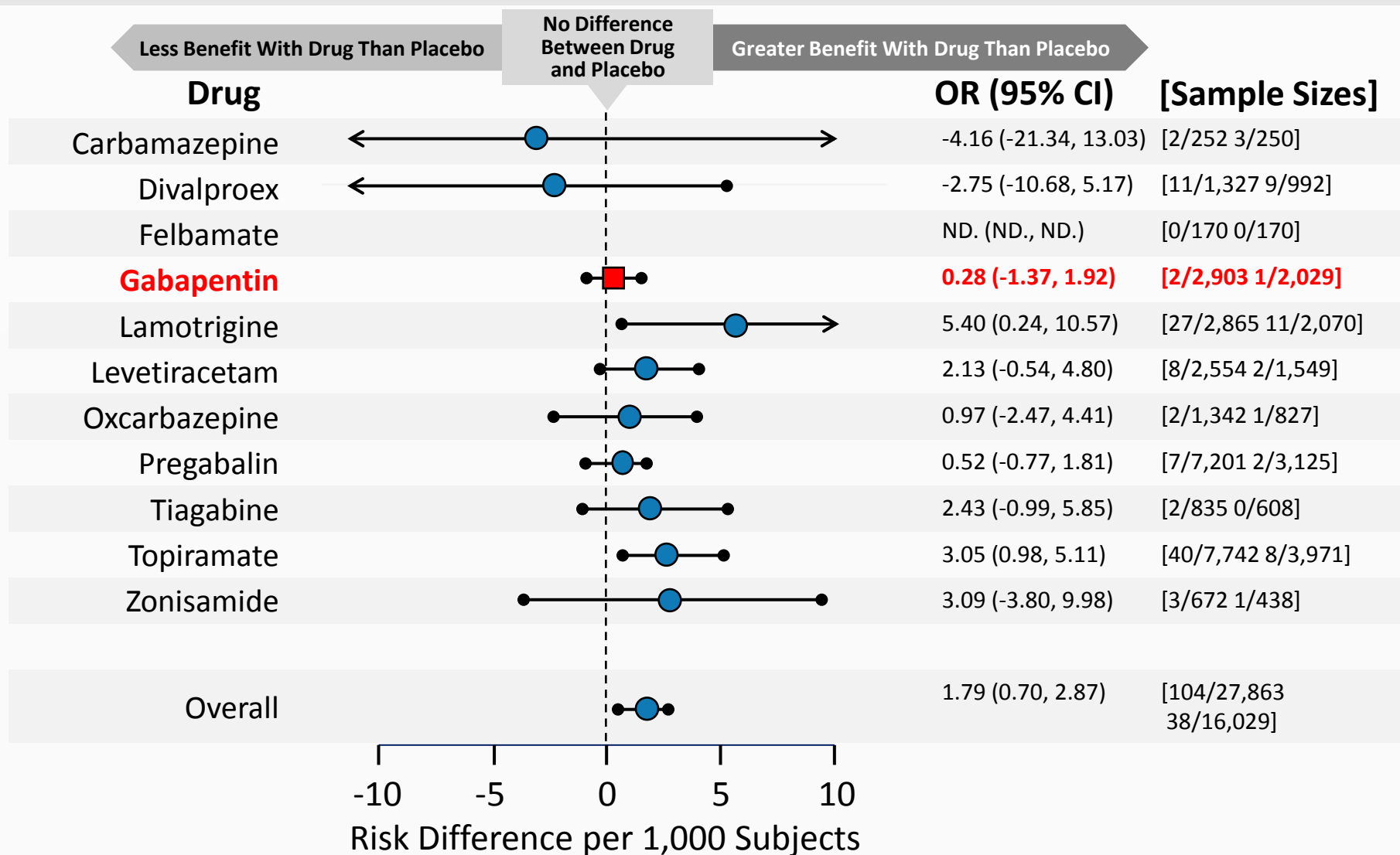
Risk Differences Relative to Placebo



Gabapentin vs. Topiramate and Lamotrigine



FDA Meta-Analysis: Risk Differences for All AEDs



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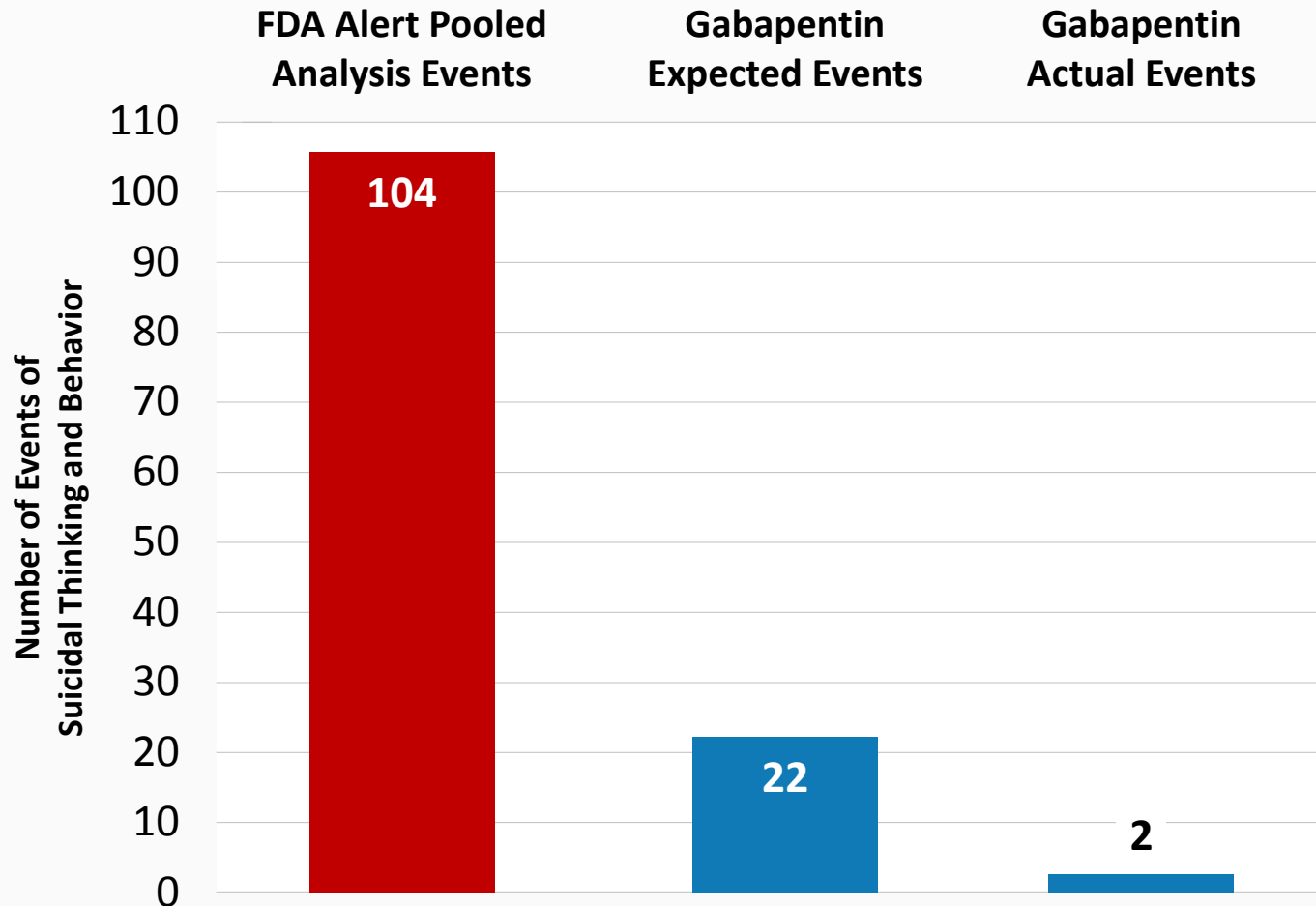
Source: Based on May 23, 2007 FDA Antiepileptic Drug Review and Evaluation of Antiepileptic Drug Toxicity, Figure 4, Pg. 26

FDA Excluded Studies With Zero Events

- Biases FDA findings toward increased risk
- Ignores significant information about safety
- Creates uncertainty as to drug effect
- Including all gabapentin data gives a more precise picture and confirms no risk

FDA Conclusions Cannot Be Applied to Gabapentin

Actual Events Far Fewer Than Expected



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Patient Groups With No Evidence Of Increased Risk

Patient Group

Gabapentin Patients → **NO**

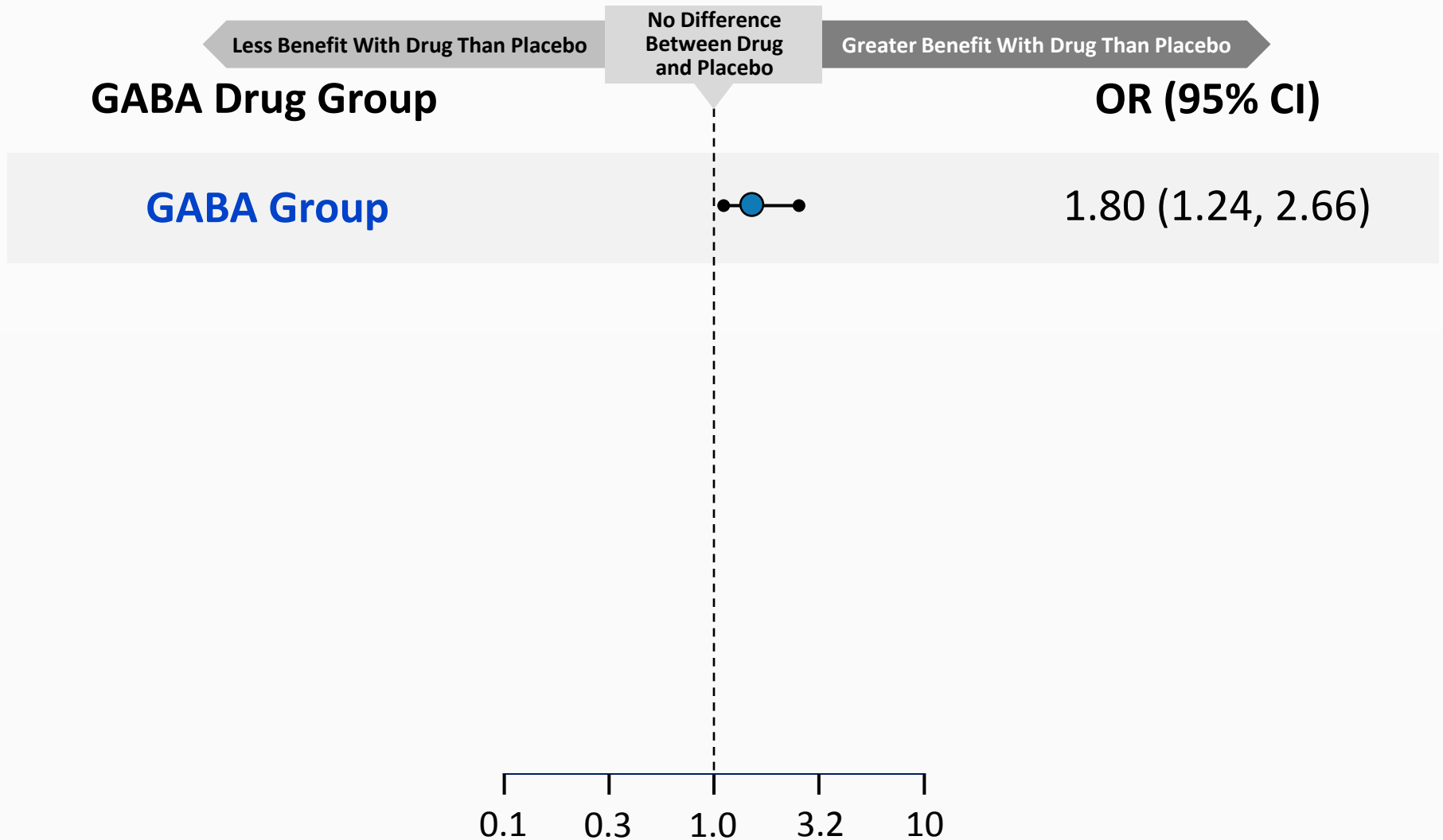
North Americans → **NO**

Psychiatric Patients → **NO**

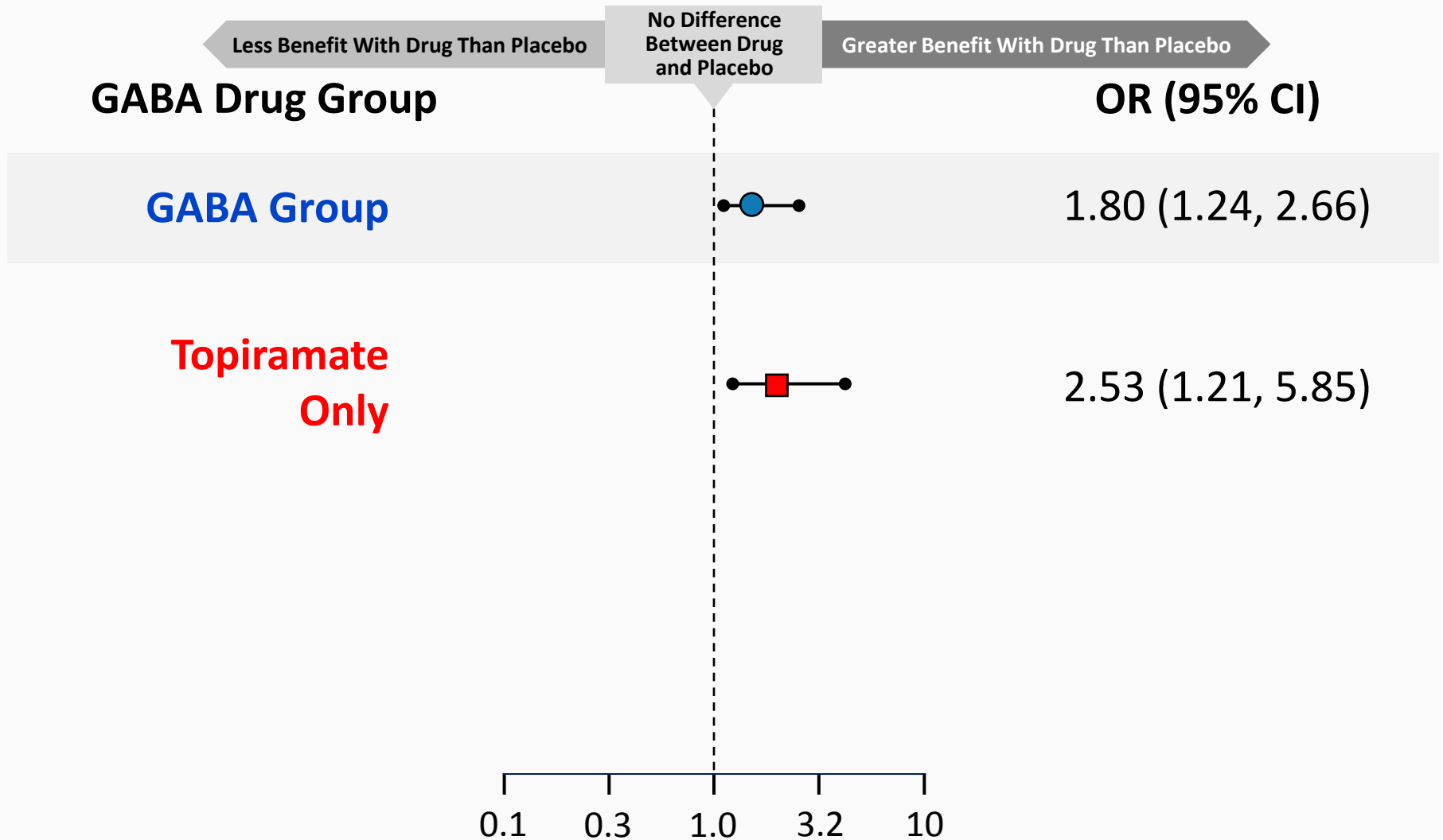
Women → **NO**

In-Patients → **NO**

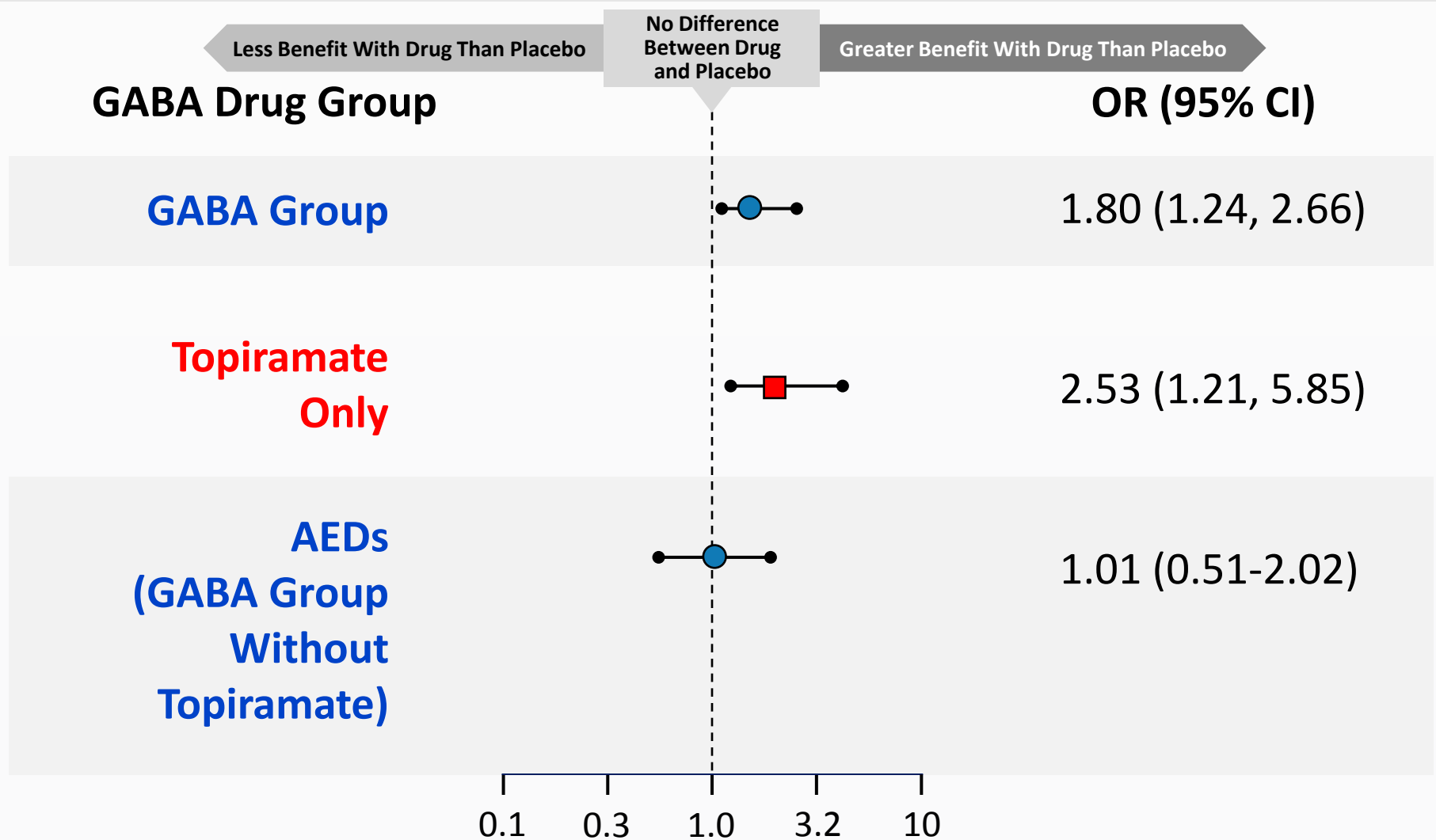
Topiramate Drove FDA Finding on GABA Drug Group



Topiramate Drove FDA Finding on GABA Drug Group



Topiramate Drove FDA Finding on GABA Drug Group



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Source: Based on May 23, 2008 FDA Public Review and Evaluation of Topiramate Drug: a. Suicidality, Figure 7, Pg. 32

FDA Acknowledges Limitations of Meta-Analysis

DR. TWYMAN: I have a question for the statisticians. Let's assume that the effect is generalizable to the class of AEDs. But, if you look at the compounds individually, could one draw the conclusion individually that compounds have a risk, or **do you need the entire data set of all the AEDs put together in order to draw the conclusion that AEDs have a signal?**

DR. LEVENSON: I would say that we need the entire data set in this case.

Gibbons, et. al 2009 Bipolar Study

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Word Count: 4343
Tables: 3
Figures: 2

The Relationship Between Antiepileptics and Suicide Attempts in Patients with Bipolar Disorder

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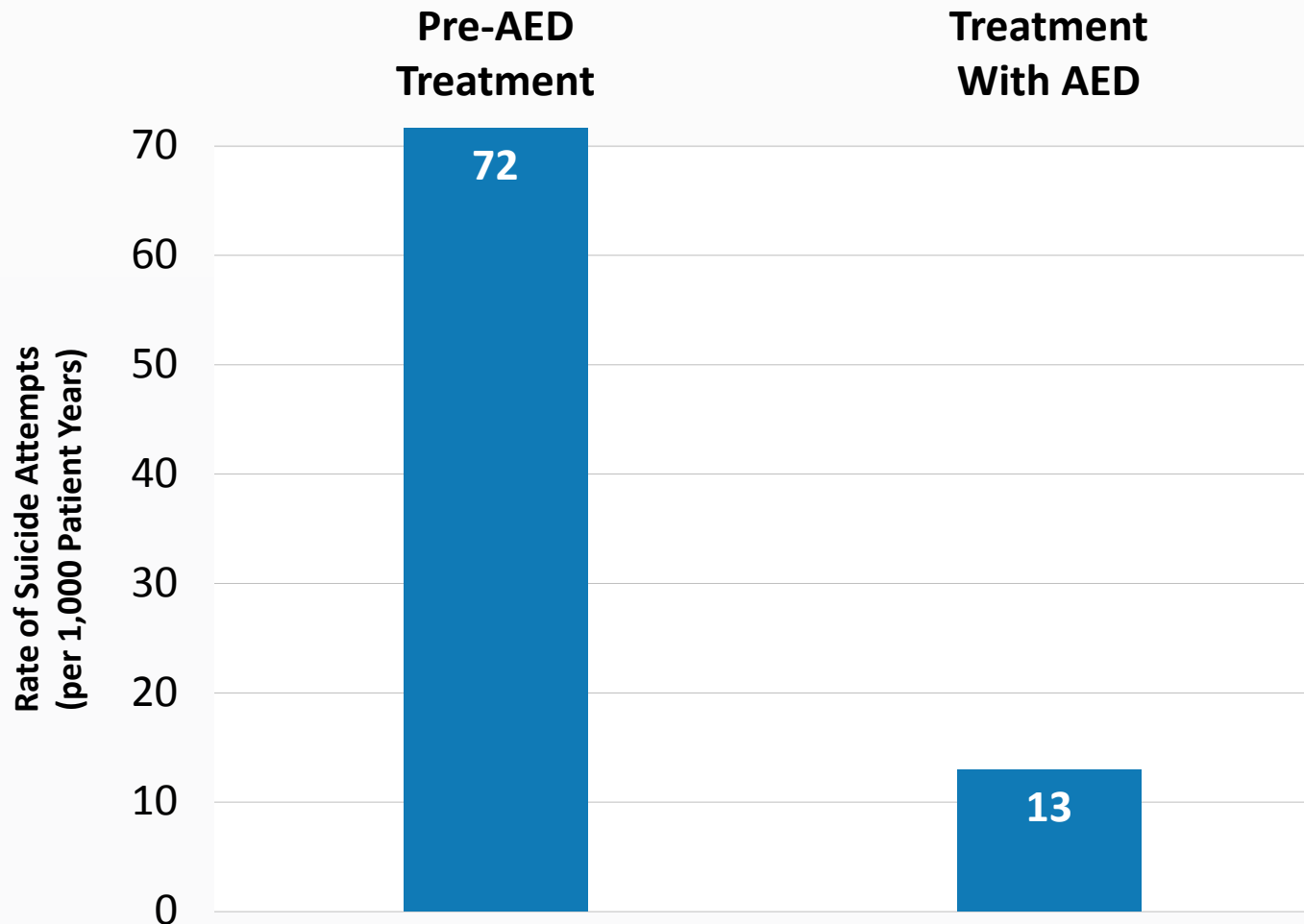
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The Relationship Between Antiepileptics and Suicide Attempts in Patients with Bipolar Disorder

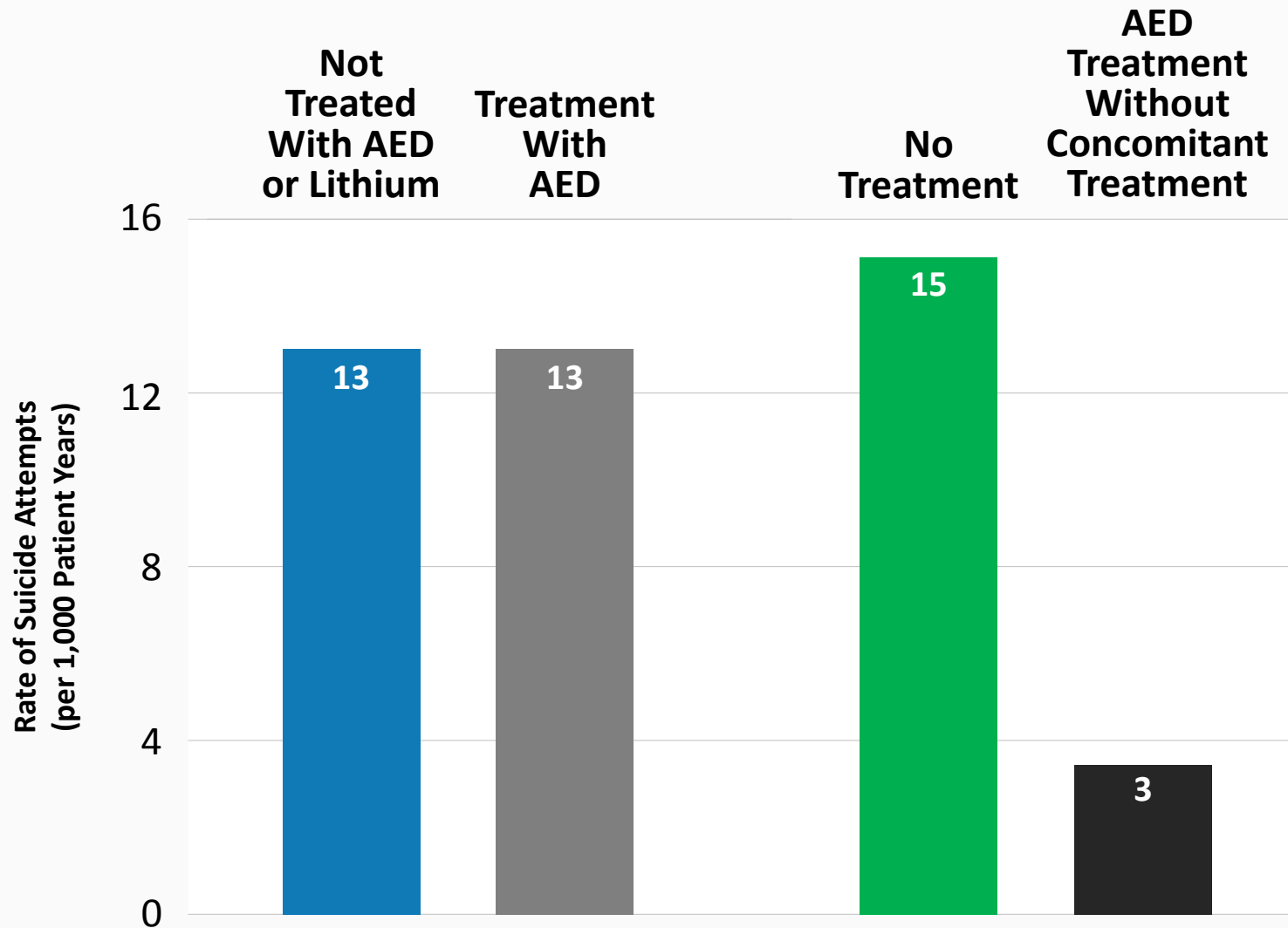
Gibbons, et. al 2009 Bipolar Study

Suicide Attempt Rate Almost Six Times Lower After AED Treatment Begins

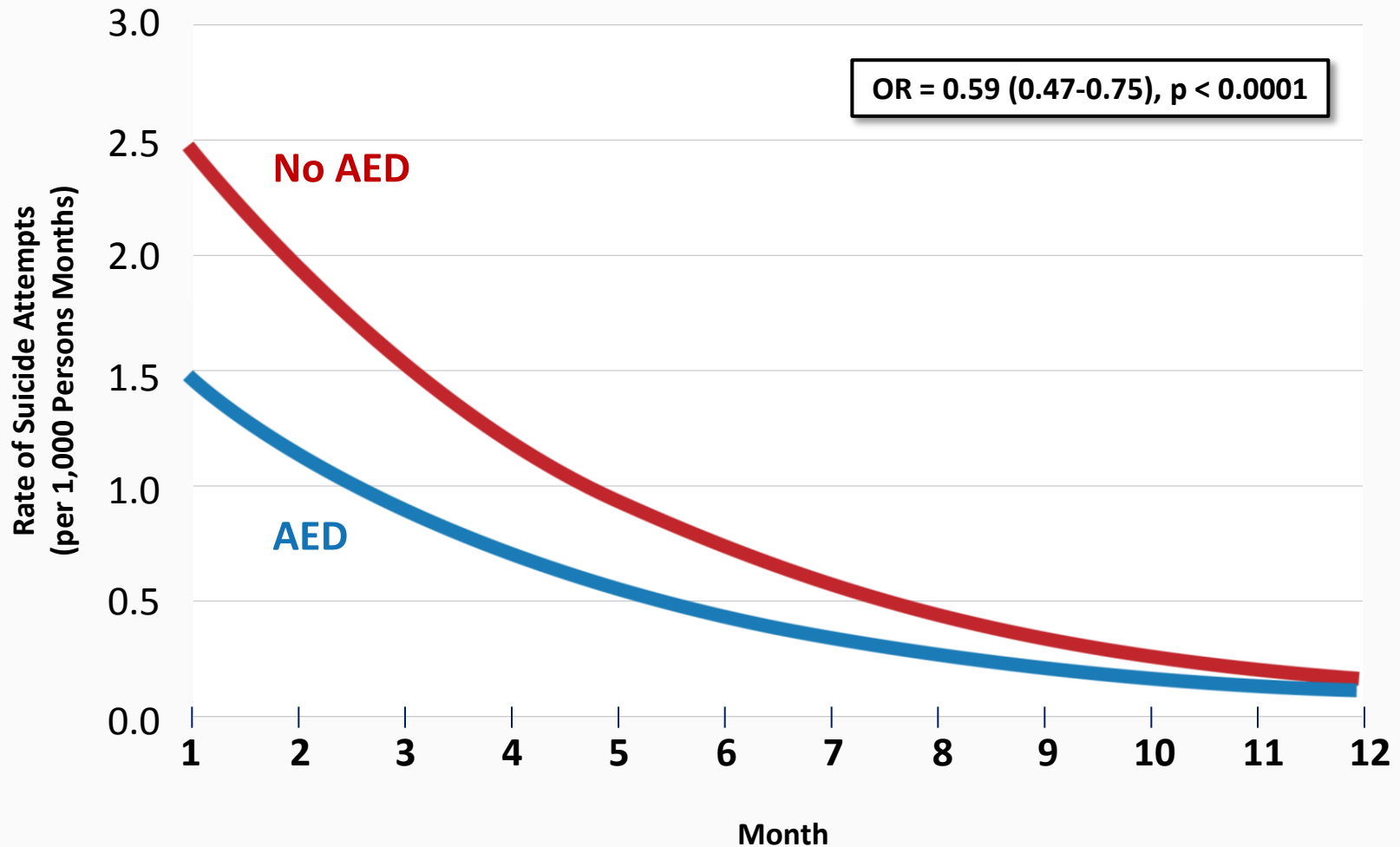


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Gibbons, et. al 2009 Bipolar Study



Gibbons, et. al 2009 Bipolar Study



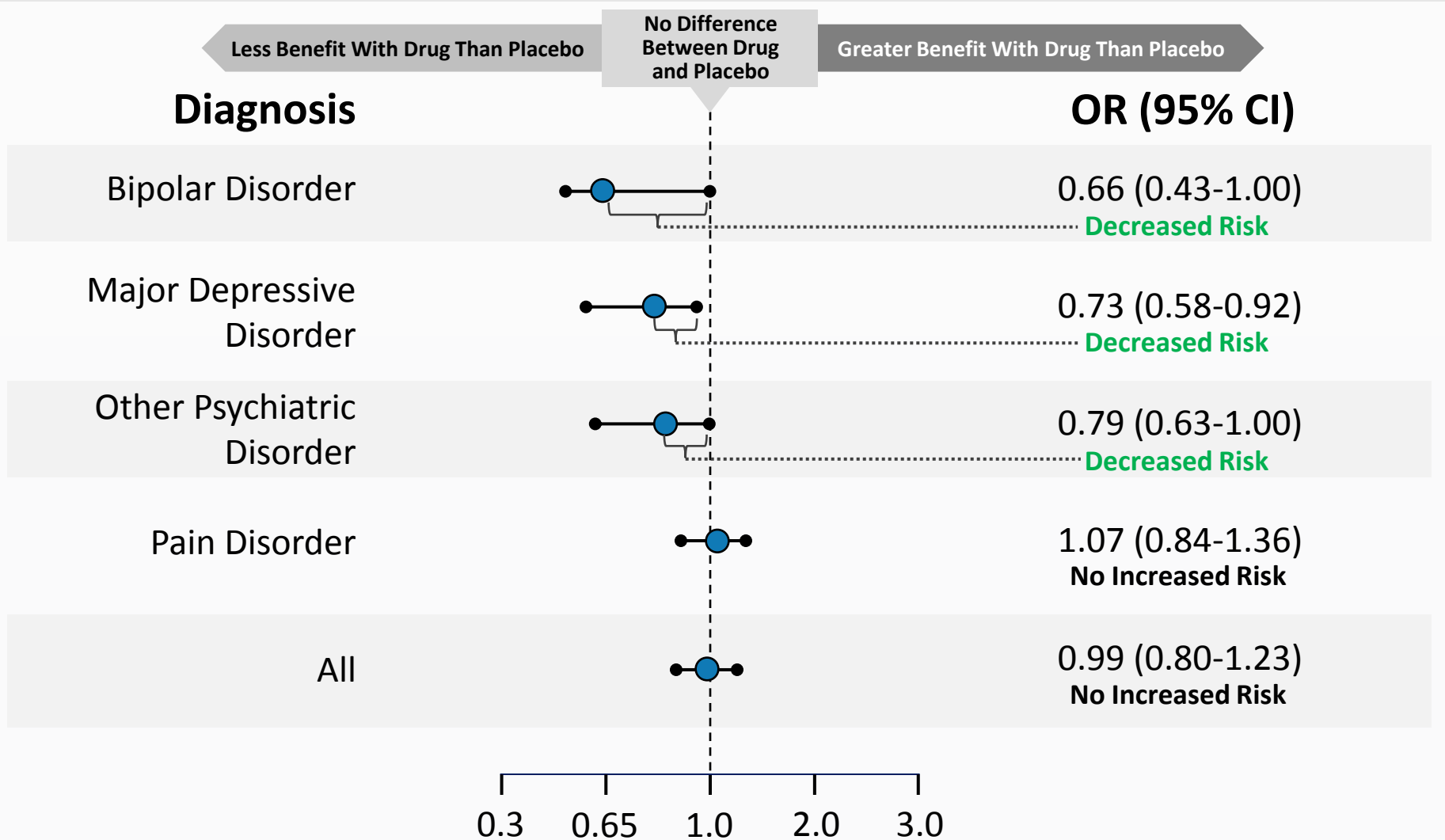
Adjusted for age, sex, concomitant medication, previous suicide attempt and year

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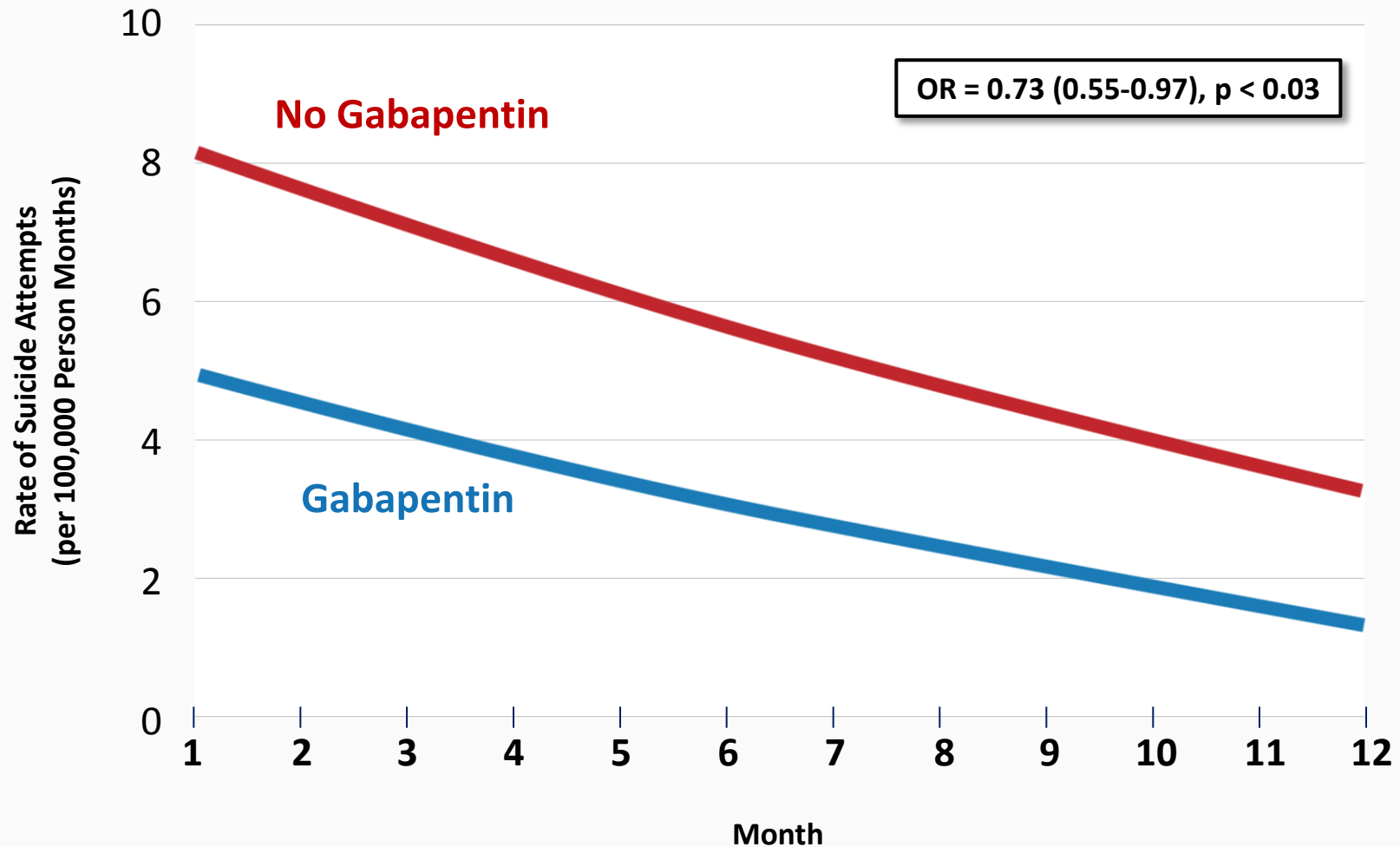
Person-Time Analysis of Highest Risk Group – Bipolar Patients With Suicide Attempt in Prior Year

- Restricting analysis to only those patients (n = 662) who made a suicide attempt in the year prior to the index diagnosis had odds ratio of 0.35 (0.17-0.74, $p < 0.005$)

Gibbons Gabapentin Study: Analysis by Group





Gibbons Gabapentin Study: Person-Time Analysis



Adjusted for age, sex, concomitant medication, diagnoses, previous suicide attempt, year and month

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Gibbons Gabapentin Study: Risk of Suicide Attempt by Group

Patient Group	Result
Bipolar	 Decreased Risk
Major Depression	 Decreased Risk
Epileptic	No Increased Risk
Pain	No Increased Risk
All Patients	No Increased Risk

Patorno: Raw and Adjusted Numbers

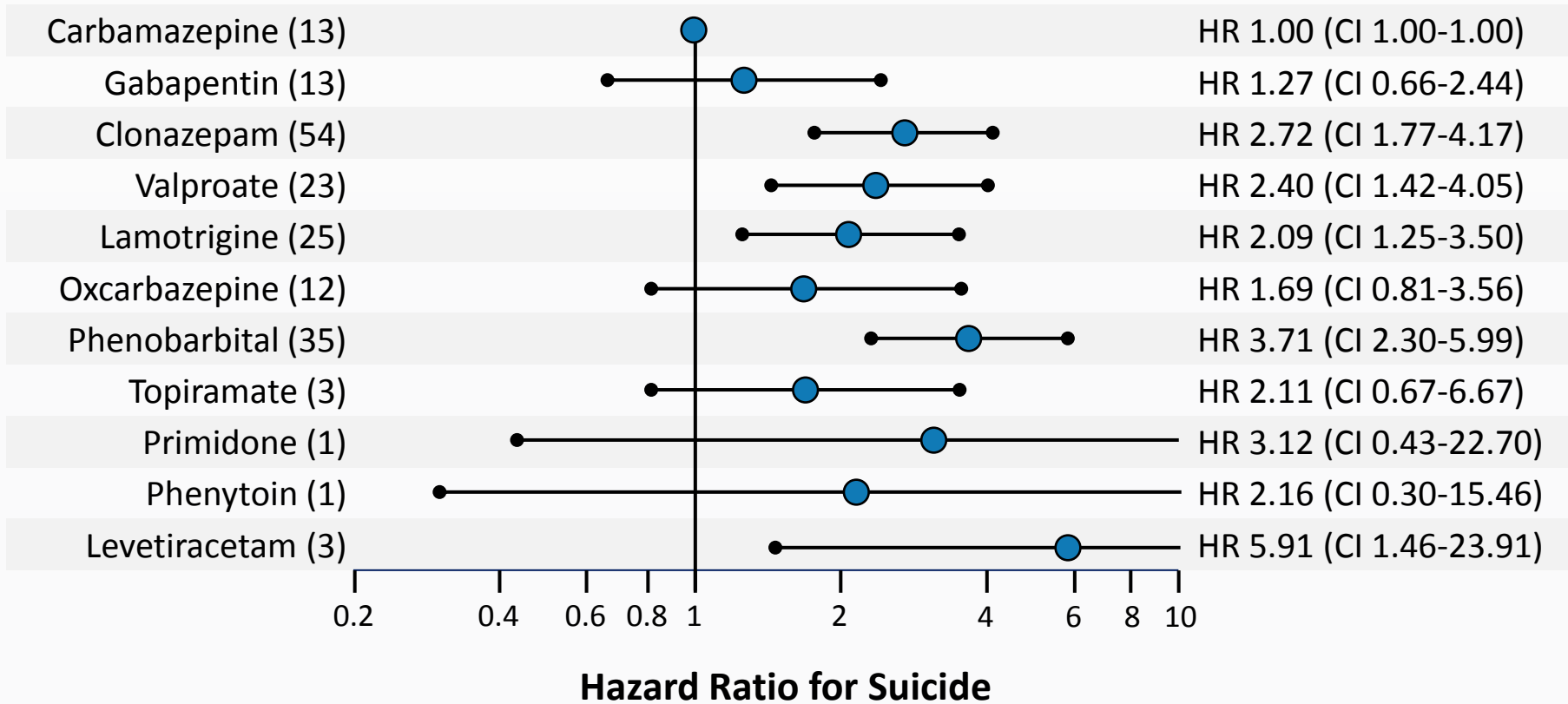
Table 4. Hazard Ratios of Study Outcomes Within 180 Days		HR (95% CI)		
		Suicide Attempt	Attempted or Completed Suicide	Attempted or Completed Suicide or Violent Death
Unadjusted Analysis	Gabapentin	0.94 (0.75-1.18)	0.95 (0.76-1.19)	0.98 (0.79-1.22)
Age-, Sex-, and Calendar Year-Adjusted Analysis	Gabapentin	1.52 (1.20-1.92)	1.48 (1.17-1.87)	1.49 (1.18-1.87)
Adjusted Analysis	Gabapentin	1.44 (1.13-1.83)	1.42 (1.11-1.80)	1.42 (1.12-1.80)

Source: Based on Table 4 of Patorno E, et al. Anticonvulsant Medications and the Risk of Suicide, Attempted Suicide or Violent Death. *Journal of Clinical Psychopharmacology*. 2010;14:1401-10

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Olesen Figure 2: Comparison With Carbamazepine

Antiepileptic Drugs and Risk of Suicide



Source: Based on Figure 2 of Olesen JB, et al. Antiepileptic drugs and risk of suicide: a nationwide study. *Pharmacology and Drug Safety*. 2010

Study	Design	Population	Compared to	Endpoint	Statistically significant difference relative to active comparator?	Statistically significant difference relative to placebo/no treatment?
FDA	Meta-analysis	Patients in RCTs	Placebo	Suicidal ideation and behavior	Not evaluated	No
Gibbons 1	Cohort	Insured patients nationwide (bipolar)	Patients not treated and no treatment periods	Suicide attempt	Not evaluated	Significant decrease following treatment
Gibbons 2	Cohort	Insured patients nationwide (gabapentin)	No treatment periods	Suicide attempt	Not evaluated	Significant decrease relative to no treatment periods
Olesen 1	Case crossover	Danish citizens age 10 and older	Times prior to event within each patient	Completed suicide	Not evaluated	No
Olesen 2	Cohort	Danish population	Carbamazepine	Completed suicide	No	Not evaluated
Paterno	Cohort	Insured patients from 14 states	Topiramate, carbamazepine	Attempted or completed suicide or violent death	Yes	Not evaluated
VanCott	Case control	Veterans age 66 and older	Phenobarbital, phenytoin, carbamazepine, valproate, lamotrigine, levetiracetam	Suicidal ideation or behavior	1. No statistically significant increase vs. any AED 2. Significant decrease vs. lamotrigine and levetiracetam	Not evaluated